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Physiology and pathophysiology of graviception

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Habilitationsschrift:

PHYSIOLOGY AND PATHOPHYSIOLOGY OF GRAVICEPTION

zur Erlangung der Venia legendi der Universität Zürich

vorgelegt von
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Zu Grunde liegende Arbeiten:

1. Tarnutzer AA, Bockisch C, Straumann D, Olasagasti I (2009). Gravity dependence of subjective visual vertical variability. J Neurophysiol 102(3):1657-71
2. Tarnutzer AA, Bockisch CJ, Straumann D (2009). Roll-dependent modulation of the subjective visual vertical: Contributions of head- and trunk-based signals. J Neurophysiol 103(2):934-41
3. Tarnutzer AA, Bockisch CJ, Straumann D (2009). Head roll dependent variability of subjective visual vertical and ocular counterroll. Exp Brain Res 195(4):621-6
4. Schuler JR, Bockisch CJ, Straumann D, Tarnutzer AA (2010). Precision and accuracy of the subjective haptic vertical in the roll plane. BMC Neurosci 14;11:83
5. Tarnutzer AA, Schuler JR, Bockisch CJ, Straumann D (2012). Hysteresis of haptic vertical and straight ahead in healthy human subjects. BMC Neurosci. 22;13(1):114
6. Bjasch D, Bockisch CJ, Straumann D, Tarnutzer AA (2012). Differential effects of visual feedback on subjective visual vertical accuracy and precision. Plos ONE 7(11):e49311
7. Tarnutzer AA, Bockisch CJ, Olasagasti I, Strauman D (2012). Egocentric and allocentric alignment tasks are affected by otolith input. J Neurophysiol 107(11):3095-106
8. Tarnutzer AA, Bockisch CJ, Straumann D (2013). Visually guided adjustments of body posture in the roll plane. Exp Brain Res. 227(1):111-20.
9. Tarnutzer AA, Fernando DP, Kheradmand A, Lasker AG, Zee DS (2012). Temporal constancy of perceived direction of gravity assessed by visual line adjustments. J Vestib Res 22(1):41-54
10. Tarnutzer AA, Fernando DP, Lasker AG, Zee DS (2012). How stable is perceived direction of gravity over extended periods in darkness? Exp Brain Res. 222(4):427-36
11. Tarnutzer AA, Schuknecht B, Straumann D (2011). Verticality perception in patients with lesions along the graviceptive pathways- Acute deficits and subsequent compensation. SANP 162 (2): 60-5
12. Tarnutzer AA, Palla A, Marti S, Schuknecht B, Straumann D (2012). Hypertrophy of the inferior olivary nucleus impacts perception of gravity. Front Neurol 3:79
13. Tarnutzer AA, Shaikh AG, Palla A, Straumann D, Marti S (2011). Vestibulocerebellar disease impairs the central representation of self-orientation. Front Neurol 2:11
14. Marti S, Tarnutzer AA, Palla A, Straumann D (2008). Preserved otolith function in patients with cerebellar atrophy and bilateral vestibulopathy. Prog Brain Res 171:211-4

SUMMARY

Herein I present a series of studies addressing the physiology and the pathophysiology of internal estimates of direction of gravity (*graviception*). Such estimates are continuously generated within an extensive network including brainstem, cerebellar, thalamic and cortical areas by integrating sensory input from various sensory organs including the vestibular organs, vision and proprioception. They can be studied at the level of the brainstem by use of reflexive eye movements and at the level of the temporo-peri-Sylvian vestibular cortex by use of psychophysics, as for example by adjusting a luminous line along perceived vertical (*subjective visual vertical, SVV*). The SVV is accurate in upright position, while in roll-tilted positions roll over-compensation (*E-effect*, for roll angles <60° and >120-135°) and roll under-compensation (*A-effect*, for roll angles >60° and <120-135°) are known. Likewise, the precision (i.e. the reproducibility) of estimates of direction of gravity decreases with increasing roll. Lesions along the bilateral pathways forwarding vestibular input to the cortex via the brainstem, cerebellum and thalamus critically affect graviception.

Why exactly estimates of direction of gravity tend to deteriorate when the subject is roll-tilted and what sensory signals and / or central computational networks drive these changes is still not known. With the aim to better understand the physiology of graviception, which is also a prerequisite to gain more detailed knowledge about deficient graviception we conducted a series of studies:

Systematic roll mis-estimations and increasing SVV variability with head-roll were previously found when roll-tilted. However, these studies were limited to roll angles of ≤150° and modeling of SVV variability assumed a linear increase of variability with roll angle. In <u>study 1</u> we extended SVV measurements to the entire roll plane. Unlike previous studies, we found an m-shaped pattern of trial-to-trial variability with peak variability around 120-135° roll and intermediate values upside-down. We concluded that assuming linearity between the roll-angle and SVV variability is not justified. Taking into account that the otolith organs contribute the most to graviception, we hypothesized that the shape of the variability curve reflects the characteristics of the otolith afferents. We created a Bayesian observer model that combines otolith input and recent experience about direction of gravity in a statistically optimal fashion. This model successfully reproduced the SVV data in terms of errors and variability, leading us to the conclusion that modulations of SVV precision in the roll plane are related to the properties of the otolith sensors and to central computational mechanisms that are not optimally tuned for roll-angles distant from upright.

In <u>study 2</u> we compared the contribution of different peripheral sensors – based on their reference system – to verticality perception. Bringing the head in a stable roll-tilted position relative to the trunk to dissociate head- and trunk-based receptors, we found superior precision and accuracy when the head was upright compared to the condition when the trunk was aligned with the gravity vector. We concluded that optimally aligning head-based sensors – i.e., the otolith organs – with gravity is most important for reliably estimating direction of gravity.

In <u>study 3</u> we compared estimated direction of gravity at the level of the cortex as required for the SVV task with ocular counter-roll (OCR) – an otolith-mediated brainstem reflex for compensating head-roll relative to gravity. We hypothesized that otolith input could be integrated for both responses, predicting a roll-angle dependent modulation of trial-to-trial variability in both systems.

A subject-by-subject comparison of SVV and OCR variability from three different roll angles was highly correlated, which led us to the conclusion that otolith input contributes to both responses.

Previous studies have proposed that the A- and E-effect are of central origin rather than due to an erroneous source signal. More specifically, the central processing of retinal input was linked to the mis-estimations. To address this hypothesis, we implemented a haptic (i.e. non-visual) task to collect serial estimates of perceived vertical in the entire roll plane and compared findings to the SVV in study 4. While both tasks showed a likely otolith-related m-shaped modulation of variability, the pattern of adjustment errors was distinct: the roll-angle had much less of an impact on the error size for the haptic task; a more less constant offset was observed for the entire roll plane. We conclude that it is the central processing of visual input that crucially affects the size of adjustment errors in graviception, while otolith input seems to be integrated in a similar fashion in both tasks. In study 4 we observed direction-dependent differences in adjustment accuracy. We therefore further evaluated possible contributing factors in study 5, including the hand used to complete the task along perceived direction of gravity and perceived straight-ahead, the subject's handedness and the type of grip. In both planes we found significant effects of the hand used and the direction of rotation, indicating that unimanual haptic tasks require control of these parameters. Furthermore, aligning objects with the perceived vertical or the perceived straight-ahead resulted in systematic direction-dependent deviations that could not be attributed to handedness, the hand used, or the type of grip. These deviations are consistent with hysteresis. Short-term adaptation shifting attention towards previous adjustment positions may provide an explanation for such biases.

As shown in study 4, visual line adjustments along perceived direction of gravity are invariably associated with roll-angle dependent errors. In study 6 we hypothesized that visual feedback may enhance SVV performance and proposed two different mechanisms – either assuming an adaptational shift of the internal estimate of direction of gravity or a higher cognitive strategy. We found that visual feedback indeed significantly improved SVV accuracy at roll angles ≥90° whereas SVV precision remained unchanged. This effect persisted for at least 18 to 24 minutes after removal of visual feedback. Noteworthy all but one subject reported consciously having added a bias to their percept of vertical to improve task performance. We concluded that the A-effect can be modulated cognitively. The dissociation between the reduced A-effect and the unchanged percept of direction of gravity speaks for a higher cognitive strategy and against the presence of underlying adaptation.

Whether otolith input is integrated only for tasks relative to gravity (gravicentric) or is used more generally for spatial orientation tasks including tasks performed in a non-gravicentric, e.g. an egocentric frame of reference is not known. In study 7 we compared alignments along gravicentric and egocentric frames in three different roll positions to address this question. Indeed a roll-angle dependent modulation of trial-to-trial variability was observed both for visual and tactile alignment tasks in egocentric and gravicentric reference frames, suggesting that independently from the frame, otolith input is integrated in spatial orientation tasks.

In study 8 we asked how well self-positioning to orientations distinct from upright can be achieved and whether visual orientation cues improve the performance of such a task. We found that in many aspects visually guided self-adjustments resemble static SVV adjustments: as in the SVV, tasks, which may theoretically be completed solely on retinal input, extra-retinal (otolithic) cues were centrally integrated. For roll-tilted positions, self-adjustments were significantly more precise in the presence of an earth-fixed visual cue compared to a body-fixed visual cue, underlining the importance of earth-stable visual input when internal estimates of gravity become more variable.

Ideally, graviception remains stable over time to allow a high test-re-test reliability. However, previous work indicated drift in perceived vertical and ocular torsion during prolonged roll. In study 9 we asked whether such perceptual drift is limited to roll-tilted positions or whether it is also present when upright – possibly to a much smaller degree as the sensors are optimized for upright position. Indeed, over five-minute blocks, significant drift in SVV was noted in about two third of the participants. Such drifts typically led to a deterioration of the adjustment accuracy. While serial correlations and central adaptation might contribute to these drifts, their origin remains largely unclear. Over the period of one hour, repetitive SVV adjustments in blocks of five minutes each revealed similar offset and drift in all blocks, as reported in study 10. This finding suggests that rather central computational mechanisms could be involved in generating drift when upright, as they emerge for repetitive blocks anew.

In study 11 we measured graviception in patients with acute lesions along the central vestibular pathways. In contrast to previous studies with such patients we extended SVV testing to roll-tilted positions, demonstrating significant increases and decreases of A- and E-effects depending on the lesion location. On follow-up graviception almost completely recovered when upright but was still deficient when roll-tilted. This led us to the conclusion that obtaining the SVV in roll-tilted positions is more sensitive to detect residual impairments in graviception.

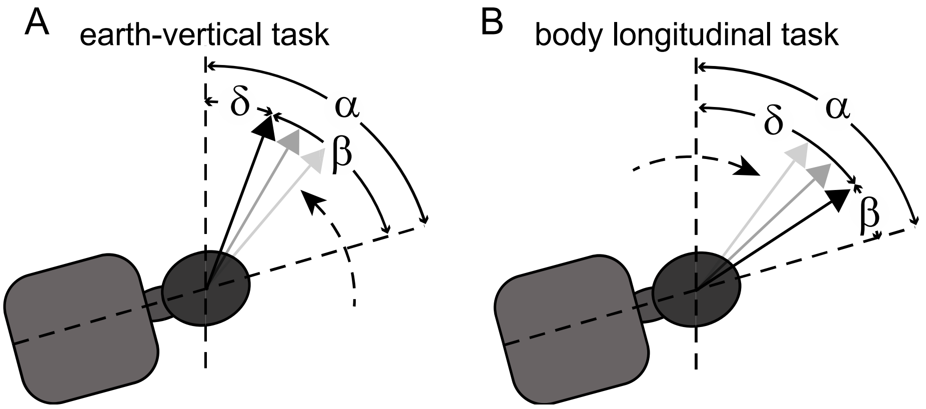
Interruption of the dentato-olivary projections, interconnecting the dentate nucleus and the contralateral inferior olivary nucleus (ION), was predicted to interfere with the dentate nucleus' role in estimating direction of gravity. In study 12 in a patient with pendular nystagmus due to hypertrophy of the ION secondary to predominantly right-sided ponto-mesencephalic hemorrhage, perceived vertical shifted from clockwise to counter-clockwise deviations within four months. We hypothesized that synchronized oscillations of ION neurons induced a loss of inhibitory control, leading to hyperactivity of the contralateral dentate nucleus and, as a result, to SVV roll to the side of the over-active dentate nucleus.

Chronic degeneration of structures involved in the processing of otolith input might also lead to impaired balance and verticality perception. This hypothesis was addressed in patients with chronic vestibulo-cerebellar disease in study 13, showing significant increases in SVV trial-to-trial variability compared to controls. We concluded that impaired balance in these patients could at least partially be explained by a less precise percept of vertical. However, vestibulo-cerebellar disease might have a distinct impact on different vestibular functions. In study 14 we reported on a series of patients with cerebellar degeneration and downbeat nystagmus presenting with loss of semi-circular canal mediated reflexes and preserved otolith-mediated reflexes. These findings suggested the existence of a dissociated pattern with severe impairment of semi-circular canal function and relatively intact otolith function in patients with cerebellar degeneration and downbeat nystagmus. This dissociation might be best explained by a predilection of atrophy for structures mainly in charge of mediating semi-circular canal function, i.e. the flocculus and the paraflocculus.

Contents

1. INTRODUCTION

This work is a collection of papers published in recent years, which elaborate the physiology and pathophysiology of internal estimates of direction of gravity (i.e., *graviception*). Accurate spatial orientation relative to gravity is achieved by integrating various sensory signals coded in distinct reference frames within the central nervous system in a weighted fashion. Thereby a continuously updated internal estimate of the direction of gravity is obtained (1). Sensory signals from the vestibular organs (utriculus, sacculus and semicircular canals), extra-vestibular (truncal) graviceptors, skin proprioceptors, vision and joint receptors are considered the most relevant contributors. These graviceptive sensory signals are forwarded to brainstem, cerebellar, thalamic and eventually cortical areas via the bilateral central vestibular pathways. Perceptual estimates of direction of gravity are frequently assessed by behavioral paradigms including line [subjective visual vertical (SVV)] and rod [subjective haptic vertical (SHV)] adjustments along perceived vertical (see Fig. 1A for details).



Legend to Figure 1 (from Tarnutzer et al. J Neurophysiol 2012): Illustration of arrow and rod adjustments in a gravicentric frame of reference (i.e. along earth-vertical, panel A) or in an egocentric frame of reference (i.e. along body-longitudinal, panel B). For a given head roll tilt α alignments along earth-vertical require compensation of head roll where β indicates the estimated roll angle relative to the body-longitudinal axis and where δ represents the deviation of the adjustments relative to earth-vertical. Whereas for perfect adjustments along earth-vertical $\beta = \alpha$ and $\delta = 0$, perfect adjustments along the body-longitudinal axis yield $\delta = \alpha$ and drive β to zero.

Whereas in positions near upright internal estimates of direction of gravity are accurate, systematic errors occur for larger roll angles. Aubert (2) was the first to observe SVV under-compensation at whole-body roll angles larger than 60° ("A-effect"), peaking around 130°, while Müller (3) was the first to report the opposite phenomenon, i.e. SVV over-compensation, at roll angles smaller than 60° ("E-effect"). At roll angles larger than 135° - 150°, SVV adjustments shift from under-compensation back to over-compensation. Use of paradigms devoid of visual input as the SHV, on the other hand, does not lead to such roll-angle dependent errors. Therefore, A- and E-effect are most likely a consequence of how distinct sensory signals are centrally combined to a unified percept of earth-vertical in the presence of visual input (4).

Research on the perception of gravity traditionally focused on the accuracy (i.e. the degree of veracity as reflected by the mean or median adjustment error), while the precision (i.e., the degree of reproducibility as reflected by the trial-to-trial variability) and the temporal stability of estimates were not thoroughly analysed. Previous research indicated that specific sensory systems might have a characteristic signal-to-noise pattern (a kind of "fingerprint") that modulates with changing orientation of the sensors with respect to gravity. An increase of noise, i.e. a larger trial-to-trial variability, was proposed for the otolith organs with increasing roll, having sharp peaks around 120 to 150° roll (4-6), however, in these studies roll angles were limited to ≤150° and the conclusions based on small numbers of trials. Modelling of SVV variability, at the same time, assumed a linearly increasing trial-to-trial variability for simplification (4), resulting in over-estimation of variability in simulations (7). Prolonged roll-tilt was associated with temporal instabilities of the percept of direction of gravity both while tilted (causing drifts) and immediately after returning back upright (leading to a post-tilt bias into the direction of previous roll) (6, 8). The origin of these drifts, however, is not known and whether such instability can also be found in upright position has not been addressed in detail.

The SVV is considered the most sensitive diagnostic test to detect lesions along the central vestibular pathways (9-14). Previous studies, however, focused on upright position. How such asymmetric lesions affect estimates of direction of gravity when roll-tilted acutely and after clinical recovery is not known. But not only acute lesions along the central vestibular pathways affect verticality perception; also slowly progressive degeneration of structures involved in the processing of vestibular input may impair graviception. Patients with vestibulo-cerebellar degeneration often present with ataxia of gait and stance. Potentially, impaired processing of vestibular input contributes to these clinical findings.

With the aim to clarify the physiology of graviception, focusing on the relative contribution of distinct sensory systems and different frames of reference used and on the temporal stability of estimated direction of gravity, and to improve our understanding how lesions along the central graviceptive pathways affect the percept of gravity we conducted a series of studies in healthy human subjects (chapter 2) and patients with acute / chronic lesions along the central vestibular pathways (chapter 4). The results of previous studies and our work allowed us to develop a computational model of verticality perception, which is able to explain the roll-angle dependent modulations of perceived direction of gravity and the contribution of the otolith organs (chapter 3).

2. GRAVICEPTION IN HEALTHY HUMAN SUBJECTS

In this chapter a selection of papers addressing the physiology of generating internal estimates of direction of gravity are presented. More specifically, we discuss various parameters, which critically influence the performance of such estimates. While chapter 2.1 focuses on the orientation of the sensory systems relative to gravity, illustrating that estimates are most reliable when the subject's head is close to upright position, we discuss the relative contribution of different sensory systems to graviception and their frames of reference in chapter 2.2. Previously distinct experimental setups used for quantifying the percept of vertical lead to different results, demanding further characterization of how changes in the way graviception is measured modulate its results. In chapter 2.3 we compare adjustments obtained by different experimental setups based on either adjusting a luminous line along perceived vertical (*subjective visual vertical* or SVV), aligning a rod along perceived vertical (*subjective haptic vertical* or SHV) by touch in complete darkness or aligning a rod along the subjective straight ahead direction (*perceived straight-ahead* or PSA) in darkness. Preliminary data indicated that repetitive measurements of perceived direction of gravity are subject to drift, i.e. that graviception is not stable over time. In a series of studies we further characterize such drift in upright position (chapter 2.4). In chapter 2.5 we address the question, whether the systematic, roll-angle dependent visual line adjustment errors can be reduced with visual feedback and what underlying mechanisms contribute.

2.1 Roll-angle dependent modulation of internal estimates of direction of gravity

Papers:

Tarnutzer AA, Bockisch C, Straumann D, Olasagasti I (2009). Gravity dependence of subjective visual vertical variability. J Neurophysiol 102(3):1657-71 (IF: 3.316)

Tarnutzer AA, Bockisch CJ, Straumann D (2009). Head roll dependent variability of subjective visual vertical and ocular counterroll. Exp Brain Res 195(4):621-6 (IF: 2.395)

While the brain integrates sensory input from different peripheral sensors including the vestibular organs (otoliths, semicircular canals), skin pressure sensors and vision to determine self-orientation relative to gravity, only the otoliths directly sense the gravito-inertial force vector. They therefore provide the major input for perceiving static head-roll relative to gravity, as measured for example by the SVV. Previous studies indicated a linear decrease of SVV precision (i.e., an increase of trial-to-trial variability defined as 1 standard deviation of individual trials) with increasing head-roll, which led to the conclusion that the effectiveness of the otolith signal is roll-angle dependent. However, the concept of "decreasing otolith effectiveness" has not been put into relation with the anatomy and the neurophysiology of the otolith organs and with the central processing of otolith input to fortify this hypothesis. Furthermore, these studies were limited in the range of roll angles studied (usually ≤120° roll) and variability was calculated from a small number of trials. Also, data collection was done sequentially for the different roll-angles, i.e., all trials at a given roll angle were collected at once. Due to drifts of SVV observed during prolonged roll-tilt, trial-to-trial variability values obtained in these studies might have over-estimated the amount of noise due to the drifts.

To clarify the possible contribution of drift to the accuracy and precision of SVV adjustments, we collected SVV adjustments in the entire roll plane and changed the subject's roll orientation after each trial. Subjects (n=7) were therefore placed in different roll orientations (0 to 360°, 15° steps) and asked to align an arrow with perceived vertical. Roll orientation was changed after each trial to avoid adaptational effects due to prolonged static roll. We found SVV variability to be minimal in upright position, increased with head-roll peaking around 120-135° roll, and decreased to intermediate values at 180° roll, consistent with an m-shaped roll-angle dependent modulation of trial-to-trial variability (see Figure 2, grey traces, in chapter 2.3 further below). This led us to the conclusion that the modulations of SVV variability was not solely due to drift related to prolonged static roll, but rather due to the properties of the peripheral receptors and / or due to central processing. With regards to the pattern of adjustment errors, we found roll-angle dependent modulations with A- and E-effects consistent with previous reports (small and inconsistent E-effects at angles < 60-75° roll; consistent A-effects at angles >60-75° and <105-135° followed by a sudden shift back to E-effects for roll angles >105-135°). In a second step we created a computational model simulating SVV accuracy and precision. This model will be discussed separately in chapter 3.

Internal estimates of direction of gravity can be studied both at the level of the brainstem by use of reflexive eye movements (e.g. compensatory counter-roll of the eyes in response to head roll, termed *ocular counter-roll* or OCR) and at the level of the cortex by use of psychophysics. Considering that estimating static head roll required for SVV (5) and OCR (15) mainly originates from the otoliths (16), we hypothesized that a shared otolith input might be reflected in a significant correlation between the variabilities of SVV and OCR. In other words, we expected that OCR variability also increased with increasing head roll. To test this hypothesis, SVV and OCR were measured simultaneous in various whole-body roll positions (upright, 45° right-ear down (RED), and 75° RED) in six subjects. Gains of OCR (defined as OCR divided by head-roll) were -0.18 (45° RED) and -0.12 (75° RED), whereas gains of compensation for body roll in the SVV task (defined as the difference between head-roll and SVV divided by head-roll) were -1.11 (45° RED) and -0.96 (75° RED). Normalized SVV and OCR variabilities were not significantly different ($p > 0.05$), i.e. both increased with increasing roll. Moreover, a significant correlation ($R^2 = 0.80$, slope 0.29) between SVV and OCR variabilities was found. We concluded that whereas the gain of OCR was different from the gain of SVV, trial-to-trial variability of OCR followed the roll dependent modulation observed in SVV variability. We proposed that the similarities in variability reflect a common otolith input, which, however, is subject to distinct central processing for determining the gain of SVV and OCR.

2.2 The integration of sensory input coded in distinct frames of reference to determine direction of gravity

<u>Papers:</u>

Tarnutzer AA, Bockisch CJ, Olasagasti I, Strauman D (2012). Egocentric and allocentric alignment tasks are affected by otolith input. J Neurophysiol 107(11):3095-106 (IF: 3.316)

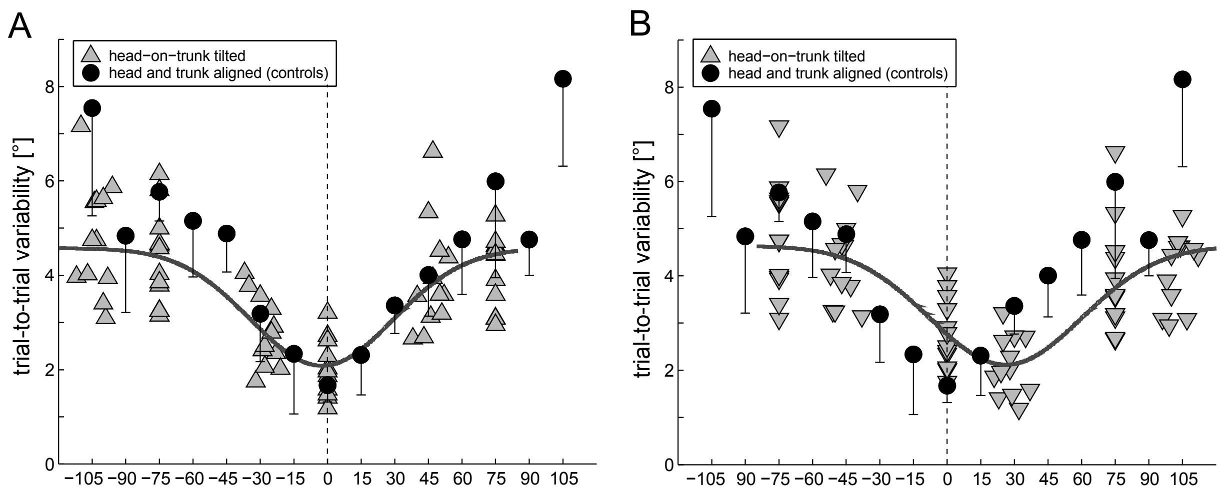
Tarnutzer AA, Bockisch CJ, Straumann D (2013). Visually guided adjustments of body posture in the roll plane. Exp Brain Res 227(1):111-20 (IF: 2.395)

Tarnutzer AA, Bockisch CJ, Straumann D (2009). Roll-dependent modulation of the subjective visual vertical: Contributions of head- and trunk-based signals. J Neurophysiol 103(2):934-41 (IF: 3.316)

Unlike for alignment tasks relative to perceived vertical (gravicentric task), graviceptive (otolithic) input is not necessarily needed for alignments relative to the perceived body-longitudinal axis (egocentric task). Whether otolith input contributes to egocentric tasks and if the roll-angle dependent modulation of variability is restricted to paradigms including visual input was not known. However, previous studies indicated that all sensory input available might be integrated to solve a specific task. Taking into account these observations we hypothesized that otolith input is integrated irrespectively of the frame of reference due to its availability to the brain. In this case, a roll-angle dependent modulation of trial-to-trial variability – considered characteristic of otolith afferents – in both egocentric and gravicentric tasks is predicted. In nine subjects we therefore compared precision and accuracy of gravicentric and egocentric alignments in various whole-body roll positions (upright, 45°, and 75° right-ear down) using a luminous line (visual paradigm) in darkness (see Figure 1). Trial-to-trial variability doubled for both egocentric and gravicentric alignments when roll-tilted. We proposed two mechanisms to possibly explain the roll-angle dependent modulation in egocentric tasks: (1) Modulating variability in estimated ocular torsion, which reflects the roll-dependent precision of otolith signals, affects the precision of estimating the line orientation relative to the head; this hypothesis predicted that variability modulation is restricted to vision-dependent alignments. (2) Estimated body-longitudinal reflects the roll-dependent variability of perceived earth-vertical. Gravicentric cues are thereby integrated regardless of the task's reference frame. To test the two hypotheses the visual paradigm was repeated using a rod instead (haptic paradigm). As with the visual paradigm, we found precision to decrease significantly with increasing head roll for both tasks. These findings led us to the conclusion that the CNS integrates input coded in a gravicentric frame to solve egocentric tasks. In analogy to gravicentric tasks, where trial-to-trial variability is mainly influenced by the properties of the otolith afferents, egocentric tasks likely integrate otolith input also. Such a shared mechanism for both paradigms and frames of reference was supported by the significantly correlated trial-to-trial variabilities. This presumed non-selectivity with regards to integrating sensory input of the CNS needs to be taken into account when interpreting the results of egocentric tasks, especially for roll-angle dependent modulations in precision, which could well be related to the otolith input.

In a follow-up study we asked whether this non-selectivity of integrating sensory input for solving static visual alignment tasks is also influencing self-positioning in space. Body position relative to gravity is continuously updated to prevent falls. Therefore the brain integrates input from the otoliths, truncal graviceptors, proprioception and vision. Without visual orientation cues estimated direction of gravity mainly depends on otolith input and becomes more variable with increasing roll-tilt. Contrary, the discrimination threshold for object orientation shows little modulation with varying roll orientation of the visual stimulus. We hypothesized that by providing earth-stationary visual orientation cues, this retinal input may be sufficient to perform self-adjustment tasks successfully, with resulting variability being independent of whole-body roll orientation. We therefore compared conditions with informative (earth-fixed) and non-informative (body-fixed) visual cues. If the brain uses exclusively retinal input (if earth-stationary) to solve the task, trial-to-trial variability will be independent from the subject's roll orientation. Alternatively, central integration of both retinal (earth-fixed) and extra-retinal inputs (termed "all sensors' integration strategy") will lead to increasing variability when roll-tilted. Subjects, seated on a motorized chair, were instructed to 1) align themselves parallel to an earth-fixed line oriented earth-vertical or roll-tilted 75° clockwise; 2) move a body-fixed line (aligned with the body-longitudinal axis or roll-tilted 75° counter-clockwise to it) by adjusting their body position until the line was perceived earth-vertical. At 75° right-ear-down position, variability increased significantly ($p<0.05$) compared to upright in both paradigms, suggesting that, despite earth-stationary retinal orientation cues, extra-retinal (otolithic) input is integrated. This finding supports the hypothesis that an "all sensors' integration strategy" might be a common feature of alignment tasks, being independent from the reference frame of the task, the presence / absence of visual input and body position. Nonetheless, the usefulness of the sensory input signals available matters: self-adjustments in the roll-tilted position were significantly ($p<0.01$) more precise for earth-fixed cues than for body-fixed cues. This underlines the importance of earth-stable visual cues when estimates of gravity become more variable with increasing whole-body roll.

The percept of direction of gravity is based on the central integration of various peripheral receptors coded in different frames of reference, e.g. relative to the head, the trunk or an extremity. Precision and accuracy of the SVV are known to modulate in the roll-plane. At large roll angles, systematic SVV errors are biased toward the subject's *body-longitudinal axis* and SVV precision is decreased. To explain this, SVV models typically implemented a bias signal based on recent experience (i.e. prior knowledge), in a *head*-fixed reference frame and assumed the sensory input to be optimally tuned along the head-longitudinal axis. To gain more insight into the relative contribution of different sensors to verticality perception we tested the pattern of SVV adjustments both in terms of accuracy and precision in experiments where the head and the trunk reference frame were not aligned. Twelve subjects were placed on a turntable with the head rolled on average by 28° counter-clockwise relative to the trunk by lateral tilt of the neck to dissociate the orientation of head- and trunk-fixed sensors relative to gravity. Subjects were brought to various roll positions (roll of head- or trunk-longitudinal axis relative to gravity: 0°, ±75°) and aligned an arrow with perceived visual vertical. We found both accuracy and precision of the SVV to be significantly ($p < 0.05$) better when the *head-longitudinal axis* was aligned with gravity (see Figure 2). Comparing absolute SVV errors for clockwise and counter-clockwise roll-tilts, statistical analysis yielded no significant differences ($p > 0.05$) when referenced relative to head-upright, but differed significantly ($p < 0.001$) when referenced relative to trunk-upright. In summary, these findings indicated that the bias signal, which drives the SVV towards the subject's body longitudinal axis, operates in a *head*-fixed reference frame. Further analysis of SVV precision supported the hypothesis that head-based graviceptive signals provide the predominant input for internal estimates of visual vertical.



Legend to Figure 2 (from Tarnutzer et al. J Neurophysiol 2010): Individual trial-to-trial SVV variability is plotted against head roll (panel A, triangles) and trunk roll (panel B, inversed triangles). Trials with clockwise and counter-clockwise arrow rotations were pooled. An inverse Gaussian function (grey line) was fitted to the data points in both reference frames to determine the head- and trunk-roll orientation with minimal variability. For comparison overall average ± 1 SD SVV variability values (black filled circles) obtained from Tarnutzer et al. J Neurophysiol 2009 with subjects having the head- and trunk-longitudinal axis aligned are shown for various roll angles, referred to as ‘controls’ in the inset. The vertical dashed line indicates head- (panel A) and trunk- (panel B) upright.

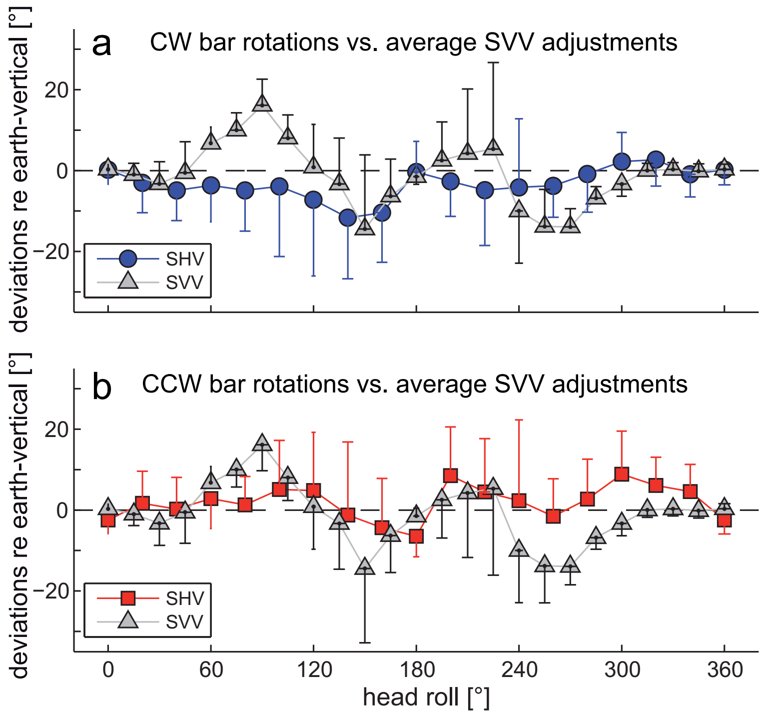
2.3 The impact of different measurement techniques on estimated direction of gravity

Papers:

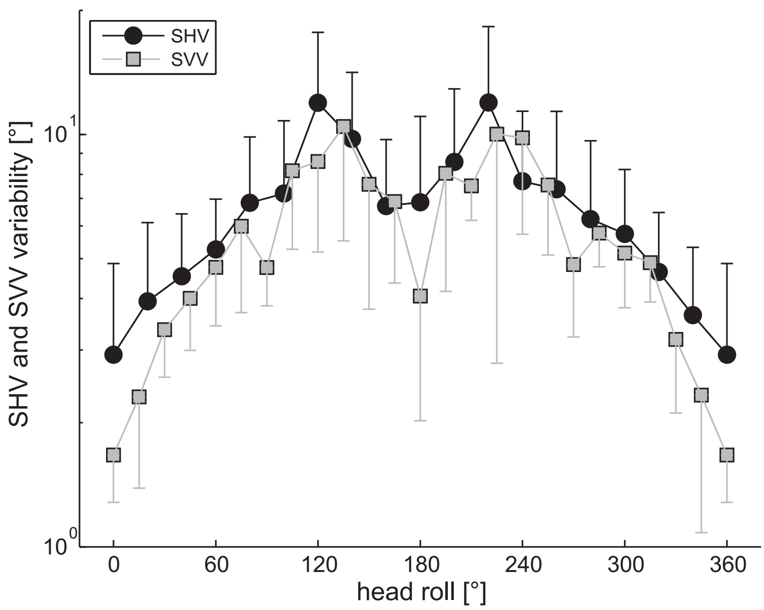
Schuler JR, Bockisch CJ, Straumann D, Tarnutzer AA (2010). Precision and accuracy of the subjective haptic vertical in the roll plane. BMC Neurosci 14;11:83 (IF: 3.042)

Tarnutzer AA, Schuler JR, Bockisch CJ, Straumann D (2012). Hysteresis of haptic vertical and straight ahead in healthy human subjects. BMC Neurosci. 22;13:114 (IF: 3.042)

When roll-tilted, the SVV deviates up to 40° from earth-vertical. Imperfections in the central processing of visual information were postulated to explain these roll-angle dependent adjustment errors. For experimental conditions devoid of visual input, e.g. adjustments of body posture or of an object along vertical in darkness, significantly smaller errors relative to earth-vertical were noted in roll-tilted positions. Whereas the accuracy of verticality adjustments seems to depend strongly on the paradigm, we hypothesized that the precision of these estimates is less influenced by the experimental setup and mainly reflects the properties of the otolith afferents (as discussed in detail in chapter 2.1). Here we measured the subjective haptic vertical (SHV) and compared our findings with previously reported SVV data. Twelve healthy right-handed human subjects adjusted a rod with the right hand along perceived earth-vertical during static head roll-tilts (0-360°, steps of 20°) in complete darkness. SHV adjustments showed a tendency for clockwise rod rotations to deviate counter-clockwise and for counter-clockwise rod rotations to deviate clockwise, indicating hysteresis. Clockwise rod rotations resulted in counter-clockwise shifts of perceived earth-vertical up to -11.7° and an average counter-clockwise SHV shift over all roll angles of -3.3° (± 11.0°; ± 1 SD). Counter-clockwise rod rotations yielded peak SHV deviations in clockwise direction of 8.9° and an average clockwise SHV shift over all roll angles of 1.8° (± 11.1°). This pattern is distinct from the roll-angle dependent modulation known from the SVV (see Figure 3 for comparison). Trial-to-trial variability was minimal in upright position, increased with increasing roll (peaking around 120-140°) and decreased to intermediate values in upside-down orientation. Compared to SVV, SHV variability near upright and upside-down was non-significantly ($p>0.05$) larger; both showed an m-shaped pattern of variability as a function of roll position (see Figure 4).



Legend to Figure 3 (from Schuler et al. BMC Neurosci 2010): Average (±1 SD) deviations of SHV (blue circles and red squares) and SVV (gray triangles, from Tarnutzer et al. J Neurophysiol 2009) in all subjects as a function of head roll. Note that trials with CW and CCW rotations of the SVV condition are pooled as no main effect for the direction of arrow rotation was previously noted. Trials with CW rod rotations (blue circles, panel A) were shifted CCW relative to trials with CCW rod rotations (red squares, panel B) in most head-roll positions. Both for trials with CW rod rotations (upper panel) and for trials with CCW rod rotations (lower panel) the modulation of adjustments within the roll plane is clearly different from average SVV adjustments, showing deviations of smaller size and little roll-angle dependency.



Legend to Figure 4 (from Schuler et al. BMC Neurosci 2010): Average (±1 SD) trial-to-trial variability of SHV (black circles) and SVV (gray squares; from Tarnutzer et al. J Neurophysiol 2009) from all subjects is shown as a function of head roll. Note that variability values are reported in a logarithmic scale. For both SVV and SHV, variability increased with increasing roll, peaked in the range of 120-150° and decreased again to intermediate values in upside-down orientation.

In summary, we found that eliminating visual orientation cues improved the accuracy of internal estimates of the direction of gravity, whereas its precision was largely unaffected. These findings underlined the important contribution of the central processing of visual input to errors in estimated earth-vertical and indicated that the precise perception of earth-verticality is dominated by the same sensory signal, i.e. the otolith signal, independent of whether the line/rod setting is under visual or tactile control. Based on the significant direction-dependent differences in adjustment errors (hysteresis, i.e. a lagging or retardation of the effect, when the forces acting on a body are changed; Merriam Webster definition) noted in the haptic modality we concluded that the control for the direction of object rotation in future studies implementing the haptic vertical is strongly recommended.

An important finding from the study by Schuler et al. (2010) was that for the SHV the direction of rotation of the haptic device had a significant impact on the accuracy of adjustments. This reported tendency for clockwise rod rotations to deviate counter-clockwise and vice versa indicated hysteresis. However, the contributing factors to this behaviour remained unclear. To clarify this we characterized the SHV in terms of handedness (right-handed vs. left-handed), hand used (right hand vs. left hand), direction of hand rotation (clockwise vs. counter-clockwise), type of grasping (wrap vs. precision grip) and gender, and compared findings with the perceived straight-ahead (PSA). Therefore, healthy human subjects repetitively performed adjustments along the SHV (n=21) and the PSA (n=10) in complete darkness. For both the SHV and the PSA significant effects of the hand used and the direction of rotation were found. The latter effect was similar for the SHV and the PSA, leading to significantly larger counter-clockwise shifts (relative to true earth-vertical and objective straight-ahead) for clockwise rotations compared to counter-clockwise rotations irrespective of the handedness and the type of grip. The effect of the hand used, however, was opposite in the two tasks: while the SHV showed a counter-clockwise bias when the right hand was used and no bias for the left hand, in the PSA a counter-clockwise bias was obtained for the left hand without a bias for the right hand. No effects of grip or handedness (studied for the SHV only) on accuracy were observed. However, SHV precision was significantly ($p<0.005$) better in right-handed subjects compared to left-handed subjects and in male subjects. Based on these observations we conclude that unimanual haptic tasks as used to determine the SHV and the PSA require control for the hand used and the type of grip as these factors significantly affect the subject's task performance. Furthermore, aligning objects with the SHV and the PSA results in systematic direction-dependent deviations that cannot be attributed to handedness, the hand used, or the type of grip. These deviations are consistent with hysteresis and are likely not related to gravitational pull, as they were observed in both planes tested, i.e. parallel and perpendicular to gravity. We hypothesize that short-term adaptation shifting attention towards previous adjustment positions may provide an explanation for such biases of spatial orientation in both the horizontal and frontal plane.

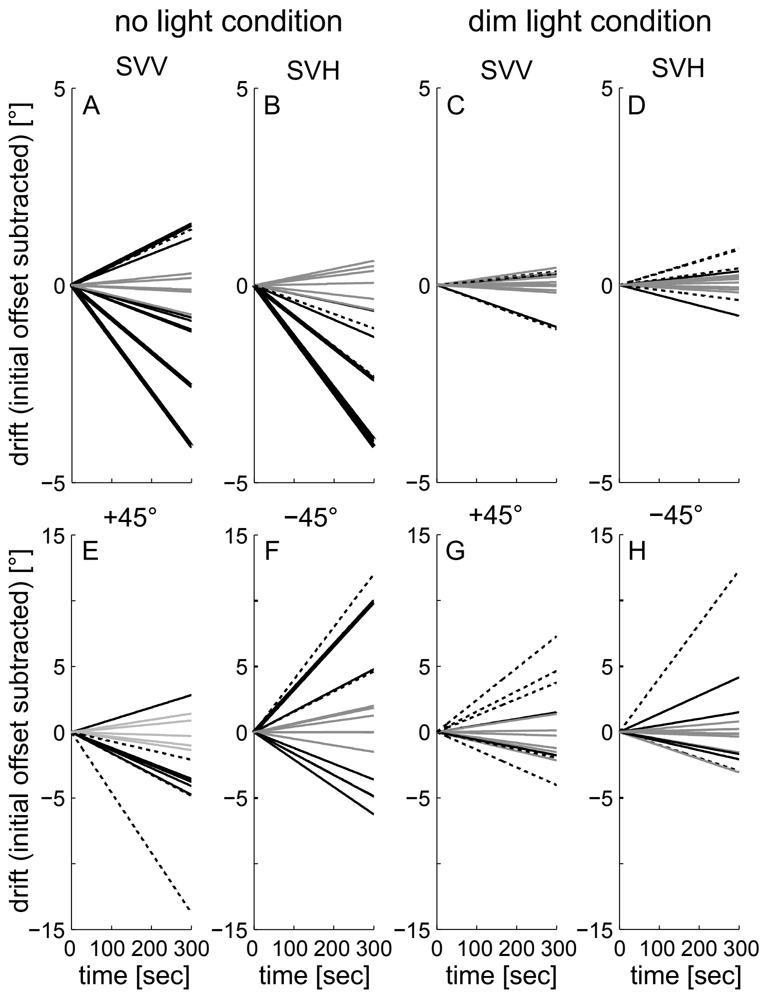
2.4 The stability of internal estimates of direction of gravity over time

Papers:

Tarnutzer AA, Fernando DP, Kheradmand A, Lasker AG, Zee DS (2012). Temporal constancy of perceived direction of gravity assessed by visual line adjustments. J Vestib Res 22(1):41-54 (IF: 1.350).

Tarnutzer AA, Fernando DP, Lasker AG, Zee DS (2012). How stable is perceived direction of gravity over extended periods in darkness? Exp Brain Res. 222(4):427-36 (IF: 2.395)

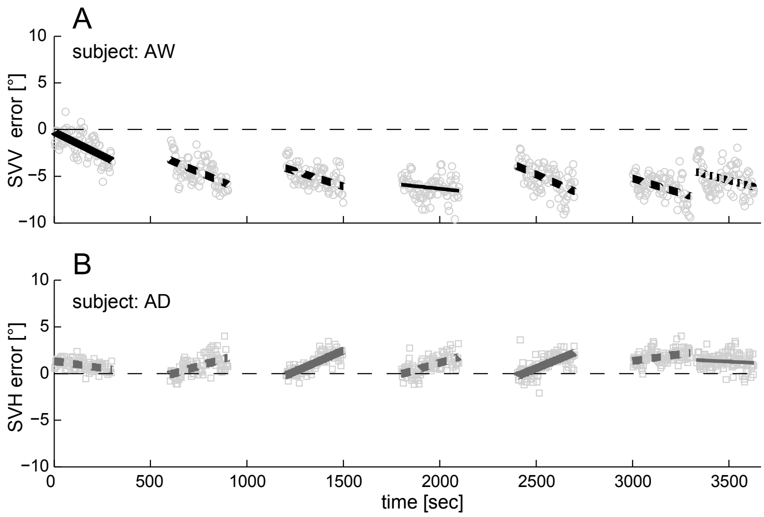
Previous work indicated drifts in perceived visual vertical during prolonged roll-tilt, however, failed to report drift when upright. Similarly, orthogonality was found between SVV and subjective visual horizontal (SVH) in upright position, whereas significant non-orthogonalities were noted when subjects were roll-tilted. We therefore decided to investigate how well internal estimates of direction of gravity are preserved over time and if the SVV and the SVH can be used inter-changeably. In comparison to previous studies we increased the sample size and conducted a subject-by-subject analysis. Fourteen human subjects repetitively aligned a luminous line to SVV, SVH or subjective visual oblique (±45°) over five minutes in otherwise complete darkness and also in dim light (Tarnutzer et al. J Vestib Res 2012). Both the accuracy and precision of adjustments along the principle axes were significantly higher than along the oblique axes. Orthogonality was only preserved in a minority of subjects. Adjustments were significantly different between SVV vs. SVH (7/14 subjects) and between +45° vs. -45° (12/14) in darkness and in 6/14 and 14/14 subjects, respectively, in dim light. In darkness, significant drifts over five minutes were observed in a majority of trials (33/56), as shown in Figure 5. Both accuracy and precision were higher if more time was taken to make the adjustment.



Legend to Figure 5 (from Tarnutzer et al. J Vestib Res 2012): Slopes representing the fit to one run of repetitive adjustments in individual subjects are shown both for darkness (panels A, B, E and F) and dim light (panels C, D, G, and H). Note that the initial offset relative to the desired roll orientation was subtracted so that all slopes start at zero offset to allow better comparison between individual subjects and facilitate illustration of the individual drifts. Traces in black refer to runs with significant ($p < 0.05$) drift, traces in grey refer to runs with non-significant ($p > 0.05$) drift. All runs with significant drift were further subdivided into three categories, depending on the goodness of fit. Black thick solid traces: $R^2 > 0.7$; black dashed traces: $0.7 > R^2 > 0.3$; black thin solid traces: $R^2 < 0.3$.

These results introduced important caveats when interpreting studies related to graviception. Specifically, they suggest that the test re-test reliability of SVV and SVH can be influenced by drift of the internal estimate of gravity. Based on spectral density analysis we found a noise pattern consistent with $1/f^{\beta}$ noise, indicating that at least part of the trial-to-trial dynamics observed in our experiments is due to the dependence of serial adjustments over time. Furthermore, using results from the SVV and SVH inter-changeably might be misleading, as many subjects do not show orthogonality even in upright position. The poor fidelity of perceived ±45° as noted in this study suggests that the brain has limited ability to estimate oblique angles. This might reflect a strategy of the brain aiming to optimize estimates along and perpendicular to gravity, as these directions contribute the most to spatial navigation and balance.

While in the previous study we noted linear drift of perceived vertical over a brief (5min) observation period, it remained unknown how such drifts change over more extensive periods of time. In a follow-up study we therefore repeated estimates of direction of gravity over a period of 60 minutes to evaluate whether drift is sustained, shows saturation or even reverses over time (Tarnutzer et al. Exp Brain Res 2012). Fifteen healthy human subjects repetitively adjusted a luminous line along SVV and SVH over periods of five minutes (constituting one block). We obtained seven blocks within 60 minutes in each subject for SVV and SVH. In-between the first six blocks subjects remained in darkness for five minutes each whereas the lights were briefly turned on before block 7. We noted significantly ($p<0.05$) increased errors in perceived direction of gravity by block 2 (SVV) and block 3 (SVH), respectively. These increases disappeared after turning on the lights before block 7. Focusing on blocks 2-6, significant drift started from similar offset positions and pointed into the same direction in a majority of runs in 9/15 (SVV) and 11/15 (SVH) subjects. Figure 6 illustrates the typical drift pattern in two individual subjects. When pooling data from all blocks, orthogonality of errors was lost in all subjects. Trial-to-trial variability remained stable over the seven runs for SVV and SVH. Only when pooling all runs, precision was significantly ($p<0.05$) higher for the SVH. Our findings suggest that perceived direction of gravity continues to fluctuate over extended recording periods with individuals showing unique patterns of direction-specific drift while variability remains stable. As subjects were upright during the entire experiment and as drift persisted over several blocks, sensory adaptation seems unlikely. We therefore favor a central origin of this kind of drift.



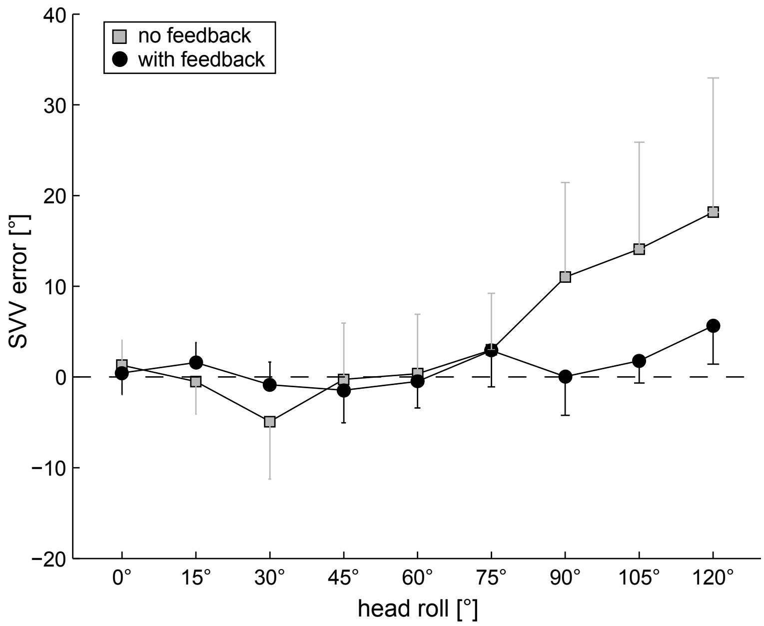
Legend to Figure 6 (Tarnutzer et al. Exp Brain Res 2012): Single subject sample data for either SVV (panel a, black lines) or SVH (panel b, grey lines) in two subjects with adjustment errors plotted against time. Robust linear regression was applied to determine the significance of drift over the individual recording periods. While thin lines refer to runs with non-significant ($p>0.05$) drift, thick lines indicate significant ($p<0.05$) drift with a further distinction based on the goodness-of-fit based on the R^2-value: thick dotted lines: $R^2<0.3$), thick dashed lines: $0.3<R^2<0.7$, and thick solid lines: $R^2>0.7$.

2.5 How visual feedback enhances the accuracy of perceived vertical

Paper:

Bjasch D, Bockisch CJ, Straumann D, Tarnutzer AA (2012). Differential effects of visual feedback on subjective visual vertical accuracy and precision. Plos ONE 7(11):e49311 (IF: 4.092)

The brain constructs an internal estimate of the gravitational vertical by integrating multiple sensory signals. Perception of gravity as measured by the SVV in darkness results in the well-known pattern of roll over-estimation (E-effect) and roll under-estimation (A-effect) of the SVV in head roll-tilted positions. These systematic misestimations are a typical feature of the luminous line paradigm. Using non-visual paradigms to indicate the perceived direction of gravity as by aligning a bar along vertical / horizontal, by self-adjustments in the roll plane or by verbal reports of whole-body roll, the A- and E-effects are greatly reduced or even eliminated. These observations suggest that the sensory signals integrated to determine the direction of gravity must be accurate, as paradigms as the subjective haptic vertical (SHV) lack the A- and E-effect. It was therefore previously suggested that the A- and E-effect reflect the downside of a strategy of the brain to optimize the precision of adjustments near upright. To better understand the mechanisms of roll over- and under-estimation we asked to which extent these adjustment errors can be modified behaviorally. Specifically, we hypothesized that visual feedback after each SVV trial results in increased accuracy, as physiological adjustment errors (A-/E-effect) are likely based on central computational mechanisms and investigated whether such improvements were related to adaptational shifts of perceived vertical or to a higher cognitive strategy. We asked 12 healthy human subjects to adjust a luminous arrow to perceived vertical in various head-roll positions (0 to 120deg right-ear down, 15deg steps). After each adjustment visual feedback was provided (lights on, display of previous adjustment and of an earth-vertical cross). Control trials consisted of SVV adjustments without feedback. At head-roll angles with the largest A-effect (90, 105, and 120deg head roll-tilt), errors were reduced significantly ($p<0.001$) by visual feedback, i.e. roll under-compensation decreased (see Figure 7), while precision of SVV was not significantly ($p>0.05$) influenced. In seven subjects an additional session with two consecutive blocks (first with, then without visual feedback) was completed at 90, 105 and 120deg head-roll. In these positions the error-reduction by the previous visual feedback block remained significant over the consecutive 18-24min (post-feedback block), i.e., was still significantly ($p<0.002$) different from the control trials. Eleven out of 12 subjects reported having consciously added a bias to their perceived vertical based on visual feedback in order to minimize errors. We conclude that improvements of SVV accuracy by visual feedback, which remained effective after removal of feedback for at least 18 minutes, rather resulted from a cognitive strategy than by adapting the internal estimate of the gravitational vertical. The mechanisms behind the SVV therefore, remained stable, which is also supported by the fact that SVV precision – depending mostly on otolith input - was not affected by visual feedback.



Legend to Figure 7 (from Bjasch et al. PLoS ONE 2012): Grand average SVV adjustment errors (± 1 SD) are plotted against head-roll for the control (in grey) and the test conditions (in black). For roll angles of 90, 105 and 120° right-ear down adjustment errors were significantly ($p<0.001$) reduced in the test condition compared to the control condition.

3. A computational model of perceived direction of gravity

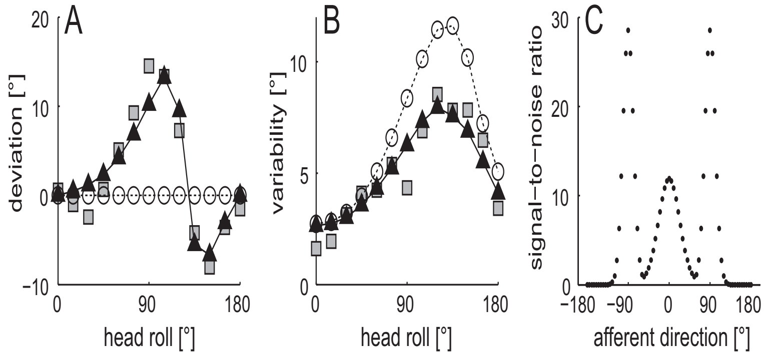
As mentioned above, previous attempts to model the SVV focused on simulating the pattern of roll-angle dependent A- and E-effects – which was achieved successfully. However, SVV trial-to-trial variability was either not addressed in these models or simulations based on the hypothetical assumption of a linear relationship between the roll-angle and the resulting trial-to-trial variability (7) without taking the properties of the involved sensory systems (mostly the otolith organs) into account. Not surprisingly, these SVV models failed to simulate the pattern of trial-to-trial variability experimentally observed, leading to overestimations of variability by a factor of approximately 2. With the following study, we aimed to develop a theory of the origin of the roll-angle dependent modulation of SVV variability. Therefore based on our knowledge and on previous anatomical and electrophysiological studies we designed a state-of-the art Bayesian observer model of SVV accuracy and precision.

<u>Paper:</u>

Tarnutzer AA, Bockisch C, Straumann D, Olasagasti I (2009). Gravity dependence of subjective visual vertical variability. J Neurophysiol 102(3):1657-71 (IF: 3.316)

To test whether the decreasing SVV precision with increasing roll-tilt angle observed could be of otolithic origin, as postulated by others, we considered the principle anatomical and neurophysiological aspects of the otolith organs and the central computational mechanisms processing this input. The aim was to study whether our simulations could reproduce the observed pattern of SVV precision and accuracy. Otolith-dependent variability was modeled by taking into consideration the non-uniform distribution of the otolith afferents and their non-linear firing rate.

The otolith-derived estimate was then combined with an internal bias shifting the estimated gravity vector towards the body-longitudinal based on recent experiences about direction of gravity. Assuming an efficient otolith estimator at all roll angles, peak variability of the model matched our data; however, modeled variability in upside-down and in upright position was very similar, which was at odds with our findings. By decreasing the effectiveness of the otolith estimator with increasing roll, simulated variability matched our experimental findings better as shown in Figure 8. We concluded that modulations of SVV precision in the roll plane are related to the properties of the otolith sensors, and to central computational mechanisms that are not optimally tuned for roll-angles distant from upright.



Legend to Figure 8 (from Tarnutzer et al. J Neurophysiol 2009): Panels A and B: illustration of deviations and intra-individual variability using the otolith-SVV model and assuming a decreasing efficiency of the otolith estimator with increasing roll angles. Both the estimated otolith-dependent deviations and variability from the otolith estimator model, including step 1 only (circles, referred to as θ_{oto} and σ_{oto} for deviations and variability, respectively), and the final SVV fits, including both step 1 and 2 (black triangles, referred to as θ_{SVV} and σ_{SVV} for deviations and variability, respectively) are compared with the experimental data (gray squares). Note that the final SVV fits match the experimental data both in terms of adjustment errors (panel A) and trial-to-trial variability (panel B).

4. Graviception in patients with brainstem and / or cerebellar lesions

Lateralized lesions along the bilateral central graviceptive pathways (interconnecting the vestibular organs with brainstem and cerebellar nuclei, the posterolateral thalamus and temporo-parietal cortical areas) lead to an imbalance of the vestibular signal and consecutively to characteristic clinical symptoms and signs. Depending on the acuteness, the extension and the location of the lesion different syndromes can be found: lateralized acute focal brainstem lesions (e.g. caused by vertebrobasilar ischemia, intracranial hemorrhage or demyelination) cause a partial or complete ocular tilt reaction (OTR; defined as ocular torsion, head tilt and skew deviation) and a tilt of the SVV. Depending on the lesion location within the brainstem ipsi-lesional (pontomedullary lesions) or contra-lesional (pontomesencephalic lesions) deviations of perceived vertical arise. The loss of certain deep cerebellar nuclei, on the other hand, more often leads to a partial OTR and either an ipsi-lesional or contra-lesional SVV roll-tilt (9). While changes in brainstem reflexes in acute focal brainstem and cerebellar lesions are well characterized, the assessment of perceptual changes was restricted to few SVV measurements in whole-body upright position in patients with acute focal lesions. Based on the tone imbalance of the otolith-mediated central pathways we hypothesized a shift of perceived direction of gravity for the entire roll-plane and collected SVV adjustments at various roll-tilt angles (chapter 4.1) in patients with acute brainstem or cerebellar lesions.

The otolith organs sense self-motion in head-fixed coordinates. However, accurate perception of self- orientation in space as well as optimal ocular motor and postural control require an estimate of motion in a space-fixed frame of reference. Self-motion is centrally transformed from head-fixed to space-fixed coordinates and is obtained by integrating multisensory (e.g., vestibular, visual, proprioceptive) input. By computing the internal estimate of direction of gravity (mainly based on otolith-input), the vestibulo-cerebellum (i.e., the flocculus, nodulus, and uvula), in particular the nodulus and the ventral uvula, facilitate this transformation. Little has been known on how diffuse bilateral cerebellar degeneration affects these otolith-mediated functions. Patients with chronic vestibulo-cerebellar disease typically demonstrate strong gravity-dependence of downbeat nystagmus (DBN). Several studies documented decreased function of the dynamic otolith-mediated translational vestibulo-ocular reflex, but static otolith-mediated functions, especially perception of gravitational vertical and static OCR in response to sustained head-tilts, have not been analyzed in patients with diffuse bilateral cerebellar degeneration. We therefore studied static otolith mediated functions in patients with vestibulo-cerebellar disease in different roll-tilt positions (chapter 4.2) and compared the extent of impairment for the different responses.

4.1 Graviception in patients with acute brainstem and / or cerebellar lesions

Papers:

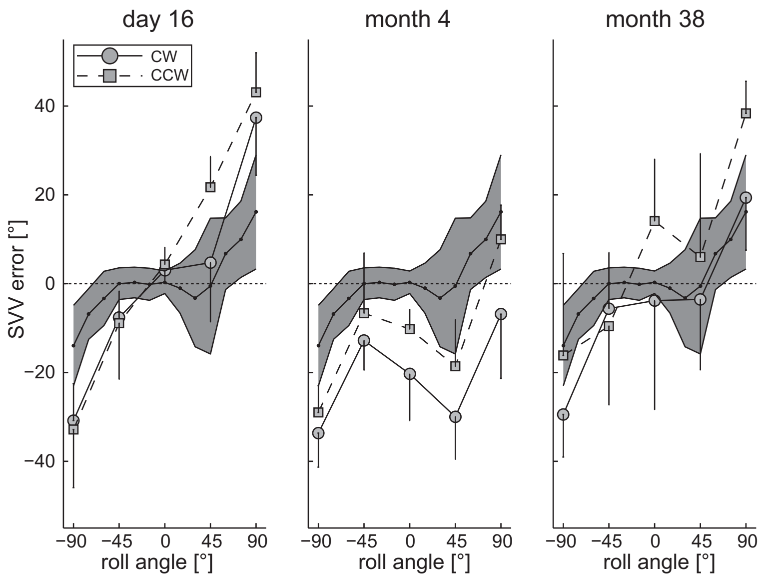
Tarnutzer AA, Schuknecht B, Straumann D (2011). Verticality perception in patients with lesions along the graviceptive pathways - Acute deficits and subsequent compensation. SANP 162 (2): 60-5 (IF: N/A)

Tarnutzer AA, Palla A, Marti S, Schuknecht B, Straumann D (2012). Hypertrophy of the inferior olivary nucleus impacts perception of gravity. Front Neurol 3:79 (IF: N/A)

Acute lesions along the central vestibular pathways (CVP) frequently lead to deviations of perceived vertical as for example assessed by the SVV. Whereas SVV errors in upright position have been well characterized, changes in the A- and E-effect and in SVV precision due to lesions along the CVP have not been studied in roll-tilted positions. In this study we reported on a series of patients with sudden CVP lesions and compared SVV measurements in different roll orientations (0°, ±45°, ±90°) in the subacute state (4-33d) with follow-up approximately four months later. In upright position, 5/6 patients showed SVV deviations in the subacute state; in 3/5 of those deviations were ipsi-lesional. When roll-tilted, 4/6 patients showed increased SVV errors compared to healthy, age-matched controls. In all patients we could explain the pattern of SVV errors by combining an SVV offset in upright position with body-position dependent errors when roll-tilted, being larger on the ipsi-lesional side and smaller on the contra-lesional side or vice versa. Compared to the healthy controls, SVV precision was decreased in 4/6 patients. After four months, verticality perception had either improved (n=1) or was within normal range (n=2) in terms of accuracy and precision in 3/4 patients. These results showed that lesions along the CVP result in altered estimates of direction of gravity in the entire roll plane that improved within few months due to central compensation. At the time accuracy had normalized in upright position, estimated direction of gravity when roll-tilted could still be erroneous (Tarnutzer et al. SANP 2011).

We concluded that the evaluation of internal estimates of direction of gravity both in terms of accuracy and precision is a sensitive means to quantify the integrity of the CVP. During rehabilitation patients with lesions along the CVP may first regain their ability to estimate direction of gravity when upright. However, they may still demonstrate difficulties (as reflected in increased A- or E-effects and larger trial-to-trial variability) in the same task when roll-tilted. When assessing the patient's behavioural skills with regards to perceived direction of gravity, restriction to upright position may under-estimate residual symptoms and may therefore lead to premature cessation of rehabilitative efforts. We therefore proposed assessing the integrity of the CVP on follow-up in various roll-tilted positions also.

Based on anatomical considerations, the interruption of the dentato-olivary projections, interconnecting the cerebellar dentate nucleus and the contralateral inferior olivary nucleus (ION), was predicted to interfere with the dentate nucleus' role in estimating direction of gravity. In a patient with pendular nystagmus due to hypertrophy of ION neurons secondary to predominantly right-sided ponto-mesencephalic hemorrhage, perceived vertical shifted from clockwise to counter-clockwise deviations within 4 months (Tarnutzer et al. Front Neurol 2012) (see Figure 9). We hypothesized that synchronized oscillations of ION neurons induced a loss of inhibitory control, leading to hyperactivity of the contralateral dentate nucleus and, as a result, to perceived vertical roll-tilt to the side of the overactive dentate nucleus.



Legend to Figure 9 (from Tarnutzer et al. Front Neurol 2012): Mean (± 1 SD) SVV adjustment errors (trials with clockwise and counter-clockwise arrow rotations analyzed separately) plotted against whole-body roll in the patient at day 16, month 4 and month 38. For comparison the grand mean (black dots) ± 2 SD of SVV adjustments from seven healthy normal control subjects [data taken from (Tarnutzer et al. J Neurophysiol 2009)]. This range covers about 95% of all values and is illustrated by the grey area.

In summary, this study further supported the crucial role of the dentate nucleus in processing vestibular information and how it is modulated by the ION. It suggests that over-excitation of the dentate nucleus by disinhibition of the ION can result in functional impairment of estimating the direction of gravity. In short, inhibition of the dentate nucleus (e.g., by an ischemic cerebellar lesion including the dentate nucleus) leads to SVV tilt away from the affected dentate nucleus (9) and over-excitation of the dentate nucleus – as reported here – leads to SVV tilt toward the affected dentate nucleus.

4.2 Graviception in patients with chronic degenerative cerebellar disease

Papers:

Marti S, Tarnutzer AA, Palla A, Straumann D (2008). Preserved otolith function in patients with cerebellar atrophy and bilateral vestibulopathy. Prog Brain Res 171:211-4 (IF: 3.040)

Tarnutzer AA, Shaikh AG, Palla A, Straumann D, Marti S (2011). Vestibulocerebellar disease impairs the central representation of self-orientation. Front Neurol 2:11 (IF: N/A)

Cerebellar degeneration affects both eye movements and vestibular function, depending on the cerebellar structures involved. For instance, with lesions of the cerebellar flocculus, the ability to adaptively modify the angular vestibulo-ocular reflex (aVOR) gain is markedly reduced, and cerebellar patients might even demonstrate severe vestibular deficits. We reported five patients (m=3, f=2) with chronic vestibulo-cerebellar disease, in whom search-coil head impulse testing revealed reduced gains of the aVOR, while sacculus-mediated myogenic potentials were normal (Marti et al. Prog Brain Res 2008). Preserved static OCR in roll-tilted positions and prominent gravity-dependent modulation of downbeat nystagmus (DBN) along the pitch plane demonstrated the integrity of otolith function in these patients as well. Based on these findings we hypothesized that, at least in some cerebellar patients with marked floccular atrophy, the dissociation between impaired semicircular canal function and preserved otolith function might be explained by a predilection of the atrophic process for the flocculus and brainstem neurons involved in aVOR gain control, while structures mediating otolith function remained widely spared by the cerebellar degeneration. The exact pathomechanism leading to the vestibular impairment, however, remained unclear: both primary multi-system-type atrophy involving cerebellar and brainstem vestibular structures as well as a mechanism of secondary retrograde degeneration of floccular brainstem target neurons mediating semicircular canal function seemed plausible.

The transformation of head-fixed otolith signals into a space-fixed frame of reference is essential for perception of self-orientation and ocular motor control. In monkeys the nodulus and ventral uvula of the vestibulo-cerebellum facilitate this transformation by computing an internal estimate of direction of gravity. These experimental findings motivated us to test the hypothesis that degeneration of the vestibulo-cerebellum in humans alters perceptual and ocular motor functions that rely on accurate estimates of gravity, such as the SVV, static OCR, and gravity-dependent modulation of vertical ocular drifts. We assessed these three parameters in 12 patients with chronic vestibulo-cerebellar disease and in ten healthy age-matched control subjects. Substantially increased trial-to-trial variability in estimated SVV was noted in the patients. Furthermore, the gravity-dependent modulation of spontaneous vertical ocular drifts along the pitch plane was significantly ($p < 0.05$) larger in the patients. However, the gain and variability of static OCR and errors in SVV were not significantly different between the patients and the controls.

In summary, we saw important implications of this study both with regards to a better understanding of self-orientation relative to gravity in degenerative cerebellar disease and to the clinical evaluation of patients with vestibulo-cerebellar disease. Compared to patients with acute unilateral cerebellar lesions, patients with slowly progressive diffuse degenerative vestibulo-cerebellar disease did not present with offsets of their internal estimates of direction of gravity, however, as a surrogate of impaired cerebellar function, their ability to control for variability of motor commands and otolith-based internal estimates was impaired. Considering the relatively intact performance in various paradigms tested in the study presented here and the slowly progressive nature of the patients' underlying cerebellar diseases, central adaptation and reweighting of multisensory input used to obtain internal estimates of direction of gravity might have – at least partially – compensated for the deficient vestibulo-cerebellar processing. Based on these findings, we propagated an assessment of the SVV in patients with gait ataxia or other clinical signs suggestive for vestibulo-cerebellar disease with a focus on determining the patient's ability to precisely estimate vertical. Also for monitoring disease progression and as an outcome parameter in treatment the SVV might be a promising tool.

5. CONCLUSIONS

Accurate and precise graviception is essential for self-orientation in space and navigation. Gravity perception, as measured by the SVV, is subject to varying precision and accuracy depending on the subject's roll orientation relative to gravity. A significant contribution of the otolith organs to the roll-angle dependent modulation of SVV precision was proposed by others, however, was not thoroughly investigated and simulated. Furthermore, the percept of vertical was known to drift during prolonged roll. The underlying mechanisms and the implications of such drift when upright, however, await more extensive research. In this work we addressed important physiological and pathophysiological aspects of estimating the direction of gravity with a focus on the processing of vestibular input. Through our studies in healthy human participants and patients with lesions along the central vestibular pathways we are able to make an essential contribution to the understanding of the integration of multisensory and especially otolith input in graviception. The results of our studies also have important diagnostic implications. The most relevant findings of this work are:

<u>*Modulation of SVV and OCR variability (studies 1 and 3):*</u> We showed that both SVV and OCR variability modulate with roll angle, most likely related to the properties of the involved peripheral receptors and central processing. Since we observed a strong correlation between SVV and OCR variability and since both parameters relied on otolith input, we conclude that the similarities in variability reflect a shared otolith input. The observed non-linear (m-shaped) relationship between the head-roll angle and the resulting SVV variability has important implications for modeling SVV accuracy and precision.

<u>*Sensory input coded in different frames of reference and its contribution to gravicentric and egocentric tasks (studies 2, 7 and 8):*</u> Both egocentric and gravicentric visual and haptic alignment tasks rely on otolith input. This suggests that the CNS integrates input coded in a gravicentric frame to solve egocentric tasks. This non-selectivity needs to be taken into account when interpreting results of egocentric tasks. Similarly, for self-adjustments in the roll plane the brain seems to take into account both retinal and extra-retinal sensory signals independently of the task, suggesting a more general nature of such an "all sensors' integration strategy". In another study we confirmed that the bias signal, which drives the SVV towards the subject's body-longitudinal axis, operates in a *head*-fixed frame and not in a trunk-fixed frame. The local maximum of SVV precision found in head-upright position when dissociating head- and trunk orientation supports the hypothesis that head-based sensors provide the predominant input for graviception.

<u>*Vision-dependence of the A- and E-effect (studies 4 and 6):*</u> Removal of visual stimuli improves the accuracy of perceived vertical by eliminating A- and E-effects. This finding underlines the impact of visual input on adjustment errors. The precision of verticality perception, however, was unaffected, which leads us to the conclusion that the same sensory input – mostly the otolith afferents – are used, independent of whether the task is under visual or tactile control. Likewise, visual feedback about adjustment performance significantly reduces the A-effect as demonstrated in the second study. The observed dissociation between a reduced A-effect and a reportedly unchanged percept of direction of gravity favors a higher cognitive strategy over true adaptation.

<u>*The temporal stability of perceived direction of gravity (studies 9 and 10):*</u> Drifts of perceived visual vertical and visual horizontal in upright position are individually distinct but stable over time, as observed in two companion studies. These drifts could not be sufficiently explained by

adaptation of sensory input or fluctuations of torsional eye position. We therefore favor an underlying central mechanism such as serial correlations.

<u>*Contributors to hysteresis in the subjective haptic vertical and the perceived straight-ahead (study 5):*</u> From this study two main conclusions can be drawn: 1) unimanual haptic alignment tasks in the frontal or axial plane require control for the hand used and the type of grip as these factors significantly affected the subject's task performance. 2) Aligning objects with the perceived vertical or the perceived straight-ahead results in systematic direction-dependent deviations that cannot be attributed to handedness, the hand used, or the type of grip. These deviations are consistent with hysteresis. We propose that short-term adaptation shifting attention towards previous adjustment positions may provide an explanation for such biases of spatial orientation.

<u>*A computational model on SVV accuracy and precision (study 1):*</u> A Bayesian observer SVV model combining otolith input and recent experience about direction of vertical in a statistically optimal fashion successfully reproduces our SVV data both in terms of errors and variability. This leads us to the conclusion that modulations of SVV precision in the roll plane are related to the properties of the otolith afferents and to central computational mechanisms that are not optimally tuned for roll-angles distant from upright.

<u>*Altered graviception due to acute lesions along the central vestibular pathways (studies 11 and 12):*</u> By extending SVV measurements to roll-tilted positions, we demonstrate that acute lateralized lesions along the central vestibular pathways affect the percept of vertical in the entire roll plane. These impairments significantly improve over months – most likely due to central compensation. At the time accuracy has normalized in upright positions, however, SVV when roll-tilted can still be erroneous. In order to reveal more subtle deficiencies in graviception and hence support continuation of balance physiotherapy we recommend SVV measurements while roll-tilted on follow-up. Noteworthy, interruption of the dentato-olivary projections interferes with the dentale nucleus' role in graviception: we propose that synchronized oscillations of inferior olivary nucleus neurons induce a loss of inhibitory control, leading to hyperactivity of the contralateral dentate nucleus and, as a result, to a pathological roll–tilt of perceived vertical to the side of the over-active dentate nucleus.

<u>*Impairments in vestibular function in patients with cerebellar disease (studies 13 and 14):*</u> Patients with vestibulo-cerebellar degeneration exhibit increased SVV variability. However, otherwise, the patients do surprisingly well, showing normal SVV accuracy and preserved ocular counter-roll gains - reflecting an intact angular vestibulo-ocular reflex. Our findings underline the robustness of the static otolith-mediated functions. Based on these results we recommend assessing the SVV in patients with gait ataxia or other clinical signs suggestive for vestibulo-cerebellar disease with a focus on determining the patient's ability to precisely estimate vertical. A subgroup of patients may present with dissociation between impaired semicircular canal function and preserved otolith function. This dissociation might be explained by a predilection of the atrophic process for the flocculus and brainstem neurons involved in angular vestibulo-ocular reflex gain control, while structures mediating otolith function remained widely spared by the cerebellar degeneration.

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7. LIST OF ABBREVIATIONS

aVOR	angular vestibulo-ocular reflex
CVP	Central vestibular pathways
ION	Inferior olivary nucleus
OCR	Ocular counter-roll
OL	Otolith
SCC	Semi-circular canals
SHV	Subjective haptic vertical
SVV	Subjective visual vertical